This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2. Synopsis

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC.
MK-0646
dalotuzumab, IV
NSCLC

CLINICAL STUDY REPORT SYNOPSIS

PROTOCOL TITLE/NO.: An Open Label, Randomized Phase I/IIa Trial Evaluating MK-0646 in Combination With Erlotinib (TARCEVA™) for Patients With Recurrent Non-Small Cell Lung Cancer #007

PROTECTION OF HUMAN SUBJECTS: This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research. [redacted]

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter (21) Worldwide [redacted]

PUBLICATION(S): WCLC2011-PN007 [redacted], WCLC abstract [redacted] AACR Meeting [redacted], Abstract #5622 [redacted]

PRIMARY THERAPY PERIOD: 31-Mar-2008 to 6-Aug-2011 **CLINICAL PHASE:** IIa

DURATION OF TREATMENT: Patients were treated with MK-0646 in combination with erlotinib or erlotinib alone until one of the following off-study criteria were met: disease progression; pregnancy; unacceptable adverse experiences; withdrawal of consent; patient noncompliance; or other events that precluded further administration of study drugs in the judgment of the investigator. Upon disease progression, patients in the erlotinib single-agent treatment arm were permitted to cross over to the combination treatment arm of erlotinib and MK-0646.

OBJECTIVE(S):

Primary:

Phase I: Determine the safety and tolerability of erlotinib in combination with MK-0646 in patients with recurrent non-small cell lung cancer (NSCLC).

Phase II: Evaluate the effect of the combination of erlotinib and MK-0646 on progression-free survival (PFS) in patients with recurrent NSCLC.

Secondary:

Radiological: Quantify response rate (RR) by Response Evaluation Criteria in Solid Tumors (RECIST).

Clinical: Determine overall survival (OS).

Tertiary:

Assess the human-anti-humanized-antibody (HAHA) response to MK-0646.

STUDY DESIGN: This was a multicenter, open-label, randomized, Phase I/IIa study of MK-0646 in combination with erlotinib administered to patients with recurrent NSCLC who previously failed at least one, but no more than two, prior chemotherapy regimens for metastatic disease. These patients should have progressed upon completion of therapy with objective radiological evidence of progression. Clinical endpoints evaluated were PFS, OS, RR, and adverse experiences (AE).

A two-part study design was applied to this study. The Phase I part of the study was a safety assessment of erlotinib in combination with MK-0646. Erlotinib was administrated orally at 150 mg once daily, and MK-0646 intravenously (IV) at 5 mg/kg weekly and then dose escalated to 10 mg/kg weekly following a 3+6 dose escalation scheme. If 10 mg/kg weekly exceeded the maximum tolerated dose (MTD), then the dose of MK-0646 to be assessed was to be 7.5 mg/kg weekly.

The dose of each drug in combination determined to be safe and tolerable in Phase I was to be used in the Phase II portion of the trial. Patients participating in Phase II were randomly assigned to one of the two treatment arms: erlotinib as a single agent or a combination of erlotinib and MK-0646.

One of the hypotheses of this study was that combination of erlotinib and MK-0646 might overcome acquired resistance to erlotinib after initial response. Therefore, upon disease progression, patients in the erlotinib single-agent treatment arm were permitted to cross over to the combination treatment arm of erlotinib and MK-0646. 14 patients who were randomized in phase-II were allowed to cross over.

[redacted]

SUBJECT/PATIENT DISPOSITION:

Table 2-1

Disposition of Patients

	MK-0646 5 mg/kg + Erlotinib (PI)		MK-0646 10 mg/kg + Erlotinib (PI)		Erlotinib		MK-0646 + Erlotinib		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	4		16		38		37		95	
Study Disposition										
DISCONTINUED	4	(100.0)	16	(100.0)	38	(100.0)	36	(97.3)	94	(98.9)
ADVERSE EVENT	0	(0.0)	1	(6.3)	3	(7.9)	3	(8.1)	7	(7.4)
LOST TO FOLLOW-UP	0	(0.0)	0	(0.0)	1	(2.6)	0	(0.0)	1	(1.1)
PHYSICIAN DECISION	0	(0.0)	0	(0.0)	4	(10.5)	0	(0.0)	4	(4.2)
PROGRESSIVE DISEASE	4	(100.0)	15	(93.8)	29	(76.3)	29	(78.4)	77	(81.1)
WITHDRAWAL BY SUBJECT	0	(0.0)	0	(0.0)	1	(2.6)	4	(10.8)	5	(5.3)
UNKNOWN	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.7)	1	(1.1)

Each patient is counted once for Study Disposition based on the latest corresponding disposition record.
UNKNOWN: A disposition record did not exist at the time of reporting.

Data Source [redacted]

Table 2-1 presents summary of discontinued patients.

[redacted].

DOSAGE/FORMULATION NOS.: Patients in the Phase I part of the study received erlotinib in combination with MK-0646. Erlotinib was administrated orally at 150 mg once daily and MK-0646 intravenously (IV) at 5 mg/kg weekly over 60 minutes and then dose escalated to 10 mg/kg weekly over 60 minutes following a 3+6 dose escalation scheme.

In phase-I, 3 patients in the 5 mg/kg cohort completed the 28-day safety assessment period without experiencing a dose limiting toxicity (DLT), less than or equal to 2 patients in the 10 mg/kg cohort experiencing a DLT, MK-0646 10 mg/kg administered weekly + erlotinib 150mg administered daily is considered safe and is being recommended for use in the Phase II portion of this study. [redacted]

Patients in Phase II were randomly assigned to one of the two treatment arms: erlotinib as a single agent or a combination of erlotinib and MK-0646 10 mg/kg weekly over 60 minutes. MK-0646 was formulated as a 20 mg/mL solution in a total volume of 12.7 mL. Patients were instructed to take erlotinib at least one hour before or two hours after the ingestion of food, since food substantially alters the bioavailability of erlotinib and may increase the risk of adverse events.

Table 2-2 presents study medication supply. Erlotinib was locally sourced.

Table 2-2

Drug Supply

Clinical Material	Potency	Dosage Form/Packaging	Batch Number (Formulation/Lot Number)
MK-0646	20 mg / mL	Solution for IV infusion	[redacted]
MK-0646	20 mg / mL	Solution for IV infusion	
MK-0646	20 mg / mL	Solution for IV infusion	
MK-0646	20 mg / mL	Solution for IV infusion	
MK-0646	20 mg / mL	Solution for IV infusion	
MK-0646	20 mg / mL	Solution for IV infusion	
MK-0646	20 mg / mL	Solution for IV infusion	
Erlotinib	150 mg	Tablet	Locally sourced
Above Information was provided by Merck Global Clinical Supply Operations.			

[redacted].

DIAGNOSIS/INCLUSION CRITERIA: Patients ≥ 18 years of age with histologically or cytologically documented, unresectable, locally advanced or metastatic, Stage IIIB/IV NSCLC that has relapsed after no more than two chemotherapy/chemoradiotherapy regimens and has not been treated with an EGFR TKI (Epidermal growth receptor tyrosine kinase) inhibitor/anti-EGFR monoclonal antibody. Patient has an Eastern Cooperative Oncology Group (ECOG) Performance status of 0 to 2 and adequate organ function.

[redacted]

EVALUATION CRITERIA:

Safety Measurements

The safety endpoints included all types of adverse experiences, laboratory safety measurements, ECOG performance scale status, and vital signs. Adverse experiences were graded and recorded throughout the study according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Toxicities were characterized in terms of duration, severity, and frequency.

Pharmacokinetic/Immunogenicity Measurements

Phase I: Pharmacokinetic (PK) parameters for MK-0646 and erlotinib.

Phase II: Serum trough concentrations of MK-0646 and human anti-humanized antibody (HAHA) to MK-0646.

Efficacy Measurements

Radiological evaluation of tumor response using diagnostic anatomic (Computed tomography (CT) or Magnetic resonance imaging (MRI)) assessment of overall disease status by categorizing radiological evaluations using RECIST, progression-free survival (PFS), and overall survival (OS).

[redacted]

STATISTICAL PLANNING AND ANALYSIS:

Data Analysis Summary

The primary endpoint of this protocol is the difference in PFS between treatment groups; this endpoint will be tested using a likelihood based approach which modifies the Cox proportional hazards model for interval censoring [redacted] This analysis is restricted to randomized patients; *i.e.,* it excludes patients in the Phase I run in. The overall (one-sided) Type 1 error for this test is 0.1. The primary clinical analysis will be done after approximately 49 patients die or experience disease progression. It is estimated 68 patients with a follow-up of approximately 5 months will be needed to reach this milestone. The study has 80% power to detect a 45.5% reduction in the hazard rate for disease progression which corresponds to a 1.84 month improvement in median PFS (assuming 2.2 month median PFS for patients in control arm).

Rates of adverse events, Grade 3/4 adverse events, and drug-related adverse events will be provided. For assessment of safety and tolerability, the proportions of patients with clinical or laboratory adverse experiences will be tabulated by treatment group. In addition to the summary results, SAS transport data tables are attached to the study report; these include results for HAHA evaluations for which no summary analyses were performed.

Secondary endpoints include OS and RR.

The study will be completed approximately 3 months after last patient discontinues study medication [redacted]

RESULTS:

Efficacy:

The primary analysis of PFS using the Finkelstein method in the full analysis set using centrally reviewed endpoints is presented in Table 2-3 and Kaplan-Meier Estimates of Progression-Free Survival Independent Radiology Review (FAS, Finkelstein's Interval Censored Method) [redacted] The hazard ratio for the MK-0646+erlotinib treatment group compared to the erlotinib group is 0.86 (1-sided p-value=0.268). Median time to PFS event is erlotinib+MK-0646 was 2.5 months compared to 1.6 months in the erlotinib only treatment group. Survival curves for time-to a PFS event shown here are using the Kaplan-Meier method; curves estimated using the Finkelstein method [redacted]

Table 2-3

Summary of Progression-Free Survival (PFS)[†] Based on Independent Radiology Review
(FAS, Finkelstein's Interval Censored Method)

	MK-0646 + Erlotinib (N=36)	Erlotinib (N=36)	MK-0646 + Erlotinib Versus Erlotinib		
			Hazard Ratio[‡]	95% CI for Hazard Ratio[‡]	p-Value[‡]
Number (%) of PFS Events	28 (77.8)	28 (77.8)	--	--	--
Person-Months	127.2	114.6	--	--	--
Event Rate/100 Person-Months (%)	22.00	24.43	--	--	--
Median PFS (Months)[§]	2.5	1.6	0.86	(0.47,1.57)	0.268
95% CI for Median PFS[§]	(1.4,5.3)	(1.3,2.7)	--	--	--

[†] Progression-free survival is defined as disease progression or death, whichever occurs first.

[‡] Finkelstein's proportional hazard model for interval censored data. P-Value is one-sided for testing H_0: HR ≥ 1 versus H_1: HR < 1.

[§] From product-limit (Kaplan-Meier) method for censored data.

Data Source [redacted]

Median overall survival of 6.9 months in the erlotinib + MK-0646 treatment group was shorter than the 14.5 month median in the erlotinib treatment group (HR=1.44, 1-sided P=.879; this is equivalent to a 2-sided p-value of 0.242); see Table 2-4 and Kaplan-Meier Estimates of Overall Survival (ITT) [redacted] Rather than the log rank test specified in the protocol, testing was performed using Cox regression.

Table 2-4

Summary of Overall Survival
(ITT)

	MK-0646 + Erlotinib (N=37)	Erlotinib (N=38)	MK-0646 + Erlotinib Versus Erlotinib		
			Hazard Ratio[†]	95% CI for Hazard Ratio	p-Value[‡]
Death (%)	23 (62.2)	20 (52.6)	--	--	--
Median Survival (Months)	6.9	14.5	1.44	(0.78,2.64)	0.879
95% CI of Median Survival	(5.2,14.7)	(8.2,.)	--	--	--
6-month Survival Rate[††]	0.57	0.69	--	--	--

[†] Estimated hazard ratio for treatment MK-0646 + Erlotinib Versus Erlotinib from Cox model.

[‡] One sided p-Value from log rank test for testing H_0: HR ≥ 1 versus H_1: HR < 1.

[††] Estimates from Kaplan-Meier curves.

Data Source [redacted]

Objective response rate by treatment group as assessed by independent radiology review is summarized in Table 2-5. There were 2 objective responses in the erlotinib group compared to 1 in the erlotinib + MK-646 group.

Table 2-5

Number (%) of Patients with Objective Response[†] Based on Independent Radiology Review (FAS)

	MK-0646 + Erlotinib (N=36)	Erlotinib (N=36)	MK-0646 + Erlotinib Versus Erlotinib		
			Difference of Rates[‡] (%)	95% CI for Differences[‡] (%)	p-Value[‡]
Number of Patients with Objective Response	1	2	--	--	--
Objective Response Rate (%)	(2.8)	(5.6)	-2.8	(-15.9,9.4)	0.721
95% Exact CI for Objective Rate (%)	(0.1,14.5)	(0.7,18.7)	--	--	--

[†] Objective response consists of confirmed complete response and confirmed partial response.

[‡] From Miettinen and Nurminen's method. One-sided p-Value for testing. H_0: Difference ≤ 0 versus H_1: Difference > 0.

Data Source [redacted]

[redacted]

Safety:

Table 2-6 presents an overall summary of clinical and laboratory adverse experiences reported for the total of 95 patients by dose level in phase-I part and arm in phase-II part. Overall, all of the patients experienced one or more adverse events except for one patient in erlotinib only arm. Percentage of patients who experienced investigator reported drug-related AE was comparable in the phase-II portion between erlotinib only arm (81.6%) and the combination arm (75.7%). Percentage of patients who experienced SAEs in phase-II part was comparable between erlotinib only arm (57.9%) and the combination arm (51.4%). Percentage of patients who experienced investigator reported drug-related SAE in phase-II part was slightly lower in the erlotinib only arm (5.3%) compared to the combination arm (13.5%). Percentage of patients who discontinued the study due to AEs in the Phase II part was similar between erlotinib only arm (26.3%) and the combination arm (27.0%). Percentage of patients who discontinued the study due to investigator reported drug-related AE in the Phase II part was comparable between erlotinib only arm (5.3%) and the combination arm (2.7%). Percentage of patients who died in the phase II part was comparable between erlotinib only arm (21.1%) and the combination arm (29.7%).

Table 2-6

Adverse Event Summary

	MK-0646 5 mg/kg + Erlotinib (PI)		MK-0646 10 mg/kg + Erlotinib (PI)		Erlotinib		MK-0646 + Erlotinib		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	4		16		38		37		95	
with one or more adverse events	4	(100.0)	16	(100.0)	37	(97.4)	37	(100.0)	94	(98.9)
with no adverse event	0	(0.0)	0	(0.0)	1	(2.6)	0	(0.0)	1	(1.1)
with drug-related† adverse events	3	(75.0)	16	(100.0)	31	(81.6)	28	(75.7)	78	(82.1)
with serious adverse events	3	(75.0)	4	(25.0)	22	(57.9)	19	(51.4)	48	(50.5)
with serious drug-related adverse events	0	(0.0)	3	(18.8)	2	(5.3)	5	(13.5)	10	(10.5)
who died	1	(25.0)	1	(6.3)	8	(21.1)	11	(29.7)	21	(22.1)
discontinued‡ due to an adverse event	0	(0.0)	3	(18.8)	10	(26.3)	10	(27.0)	23	(24.2)
discontinued due to a drug-related adverse event	0	(0.0)	1	(6.3)	2	(5.3)	1	(2.7)	4	(4.2)
discontinued due to a serious adverse event	0	(0.0)	2	(12.5)	6	(15.8)	8	(21.6)	16	(16.8)
discontinued due to a serious drug-related adverse event	0	(0.0)	1	(6.3)	2	(5.3)	0	(0.0)	3	(3.2)

† Determined by the investigator to be related to the drug.

‡ Study medication withdrawn.

Data Source: [redacted]

The AEs for all toxicity grades that were most commonly reported (in at least 20% of patients) [redacted] were diarrhea (73.7%), rash (62.1%), nausea (41.1%), decreased appetite (54.7%), asthenia (41.1%), fatigue (28.4%), dyspnoea (27.4%), constipation (26.3%), vomiting (23.2%), pruritus (23.2%), hyperglycemia (21.1%), pyrexia (20.0%), dermatitis acneiform (20.0%), dry skin (20.0%).

The AEs of all toxicity grades that were most commonly reported as drug-related by investigators (in at least 10% of patients) included diarrhea (47.4%), rash (47.4%), dermatitis acneiform (16.8%), nausea (13.7%), xeroderma (13.7%), dry skin (12.6%), pruritus (12.6%), decreased appetite (11.6%), asthenia (11.6%), and paronychia (10.5%) [redacted].

The AEs with a toxicity ≥ Grade 3 that were most commonly reported [redacted] were hyperglycemia (13.7%), non-small cell lung cancer (12.6%) (This term was used for disease progression), diarrhea (6.3%), asthenia (5.3%) and rash (5.3%).

The AEs with a toxicity ≥ Grade 3 that were most commonly reported as drug-related by investigators were hyperglycemia (6.3%), rash (5.3%) and diarrhea (4.2%) [redacted].

Percentage of patients who experienced at least one of investigator-reported clinical AEs of hyperglycemia, increased blood glucose, hypoglycemia, and decreased blood glucose was higher in arms with MK-0646 compared to erlotinib only arm [redacted]

In addition, data analysis was also performed to evaluate the incidence of increased or decrease serum glucose in the evaluable patients during the treatment and post-study period. These patients should have had both baseline and post-study (the first 16 days post-dose) glucose test results available and the data analysis captured the most severe post baseline grade.

Percentage of evaluable patients who experienced the incidence of hyperglycemia detected by increased serum glucose test was comparable between erloninib only arm (68.0%) and arms with MK-0646 (50.0%, 64.0% and 78.6%) [redacted]

Percentage of patients who experienced at least one of clinical AE related to hearing loss was reported by two patients in phase-II MK-0646 + erlotinib arm. [redacted]

The SAEs that were most commonly reported for all toxicity grades were non-small cell lung cancer (13.7%) (This term was used for disease progression), pneumonia (7.4%), and hyperglycemia (3.2%). [redacted]

One (1) death was reported by the investigator as related to study drug in erlotinib only arm: [redacted]

CONCLUSIONS: In this study, MK-0646 did not appear to add benefit to the standard therapy (erlotinib) for patients with recurrent non-small cell lung cancer. Results from the Phase IIa portion of PN007 did not meet the pre-specified criteria for proof-of-concept (one-sided p-value < 0.10 for the test of treatment effect on progression-free survival). More patients in the experimental arm had adverse experiences than in the control arm. However, the interpretation of safety and tolerability data in the phase-II part may be compromised by cross-over.

AUTHORS: [redacted]